



NTP
National Toxicology Program

Toxicology and Carcinogenesis Studies of
Goldenseal Root Powder (*Hydrastis canadensis*)

Dr. June K. Dunnick
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors
Technical Reports Review Subcommittee Meeting

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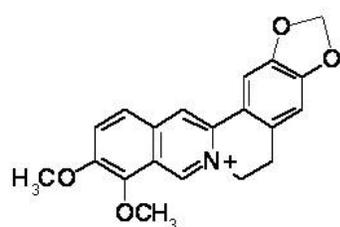


Nomination of Goldenseal Root Powder

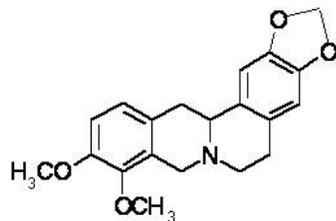
- Nominated by NIEHS as part of a review of herbal medicines
- Used in folk medicines for treatment of GI disturbances, inflammation, and proposed anticancer activity
- Children taking nonvitamin/nonmineral natural products often use goldenseal (Barnes et al, 2008)
- One of the 10 most widely sold herbal medicines in the U. S. (Blumenthal, 1999)



Major Alkaloid Constituents of Goldenseal



Berberine



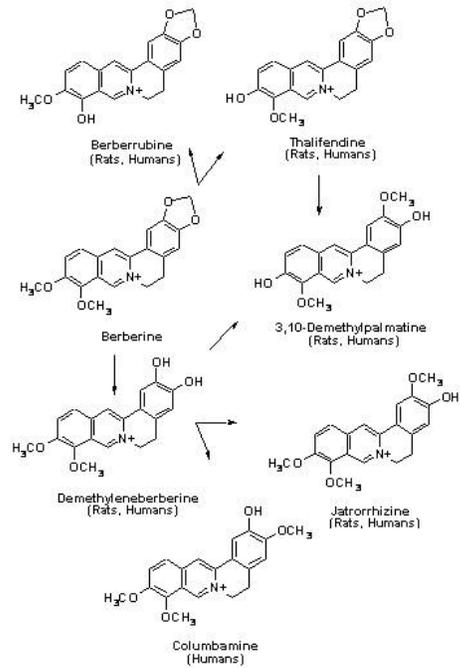
Canadine



Hydrastine



Berberine Metabolites in Rats and Humans





Genotoxicity Data

- Goldenseal
 - Salmonella - negative
 - Micronucleus - negative
- Berberine
 - Salmonella - negative
 - Micronucleus - negative
- Topoisomerase inhibition
 - Berberine and berberine metabolites - positive



Goldenseal Study Design

- Study Animals: Male and female F344/N rats & B6C3F1 mice
- Route: feed
- 14-Day studies:
 - 5 animals/species/sex/dose
 - Rats & Mice: 0, 1560, 3125, 12,500, 25,000, 50,000 ppm
- 13-Week Studies:
 - 10 animals/species/sex/dose
 - Rats & Mice: 0, 1560, 3125, 12,500, 25,000, 50,000 ppm
- 2-Year Studies:
 - 50 animals/species/sex/dose
 - Rats & Mice: 0, 3000, 9000, 25,000 ppm



14-day Studies - Rats & Mice

Dose (ppm)	0	1560	3125	6250	12,500	25,000	50,000
Male rats							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	101	101	100	100	98	96
Liver wt (% control)	-	109	111	123**	132**	141**	149**
Female rats							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	97	100	96	98	98	98
Liver wt (% control)	-	98	105	110	117**	122**	137**
Male mice							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	99	101	99	96	100	93
Liver wt (% control)	-	99	102	101	108	123**	136**
Female mice							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	100	99	97	98	102	99
Liver wt (% control)	-	100	92	108	96	101	119**

*Differs from the control group at ** $p \leq 0.01$

N=5 per group



14-day Studies - Rats & Mice

Dose (ppm)	0	1560	3125	6250	12,500	25,000	50,000
Male rats							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	101	101	100	100	98	96
Liver wt (% control)	-	109	111	123**	132**	141**(H)	149**(H)
Female rats							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	97	100	96	98	98	98
Liver wt (% control)	-	98	105	110	117**	122**(H)	137**(H)
Male mice							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	99	101	99	96	100	93
Liver wt (% control)	-	99	102	101	108	123**	136**(H)
Female mice							
Survival	5	5	5	5	5	5	5
Body wt (% control)	-	100	99	97	98	102	99
Liver wt (% control)	-	100	92	108	96	101	119**(H)

H = hepatocellular hypertrophy

N=5 per group



13-Week Studies - Survival, Body Wts, & Liver Wts - Rats & Mice

Dose (ppm)	0	3125	6250	12,500	25,000	50,000
Male rats						
Survival	10	10	10	10	10	10
Body wt (% control)	-	100	101	103	98	90*
Liver wt (% control)	-	109	119**	130**	137**	140**
Female rats						
Survival	10	10	9	10	10	10
Body wt (% control)	-	105	100	98	98	94*
Liver wt (% control)	-	121**	116**	128**	145**	159**
Male mice						
Survival	10	10	10	10	10	10
Body wt (% control)	-	99	100	102	98	94
Liver wt (% control)	-	103	106	114**	122**	143**
Female mice						
Survival	10	10	10	10	10	10
Body wt (% control)	-	101	103	100	92*	86**
Liver wt (% control)	-	99	103	99	111**	111**

Differs from the control group at * $p \leq 0.05$ ** $p \leq 0.01$

N=10 per group



13-Week Studies - Liver Lesions - Rats & Mice

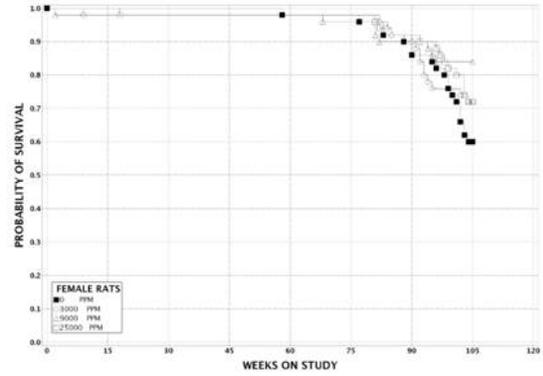
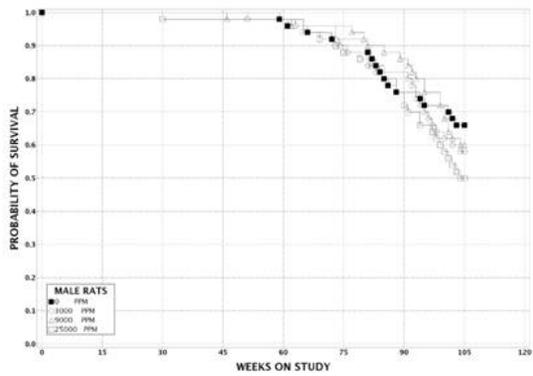
Dose (ppm)	0	3125	6250	12,500	25,000	50,000
Male rats						
Hepatocyte, Hypertrophy	0	0	2 (1.0) ^a	9** (1.0)	10** (1.3)	10** (1.8)
Hepatocyte, vacuolization cytoplasmic	1 (1.0)	10** (1.0)	10 (1.0)	10** (1.0)	10** (1.0)	10** (1.0)
Female rats						
Hepatocyte, Hypertrophy	0	0	3 (1.0)	10** (1.0)	10** (1.9)	10** (2.0)
Male mice						
Hepatocyte, Hypertrophy	0	0	0	4* (1.0)	10** (1.9)	10** (2.3)
Female mice						
Hepatocyte, Hypertrophy	0	0	0	9** (1.0)	10** (2.3)	10** (2.6)

^aSeverity Grade *p ≤ 0.05 **p ≤ 0.01

N=10 per group

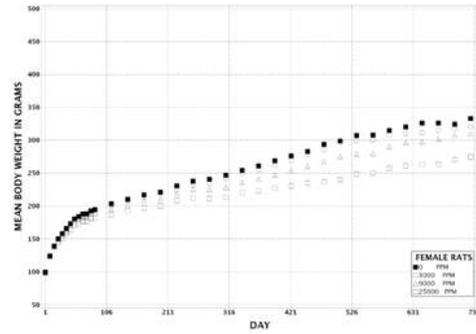
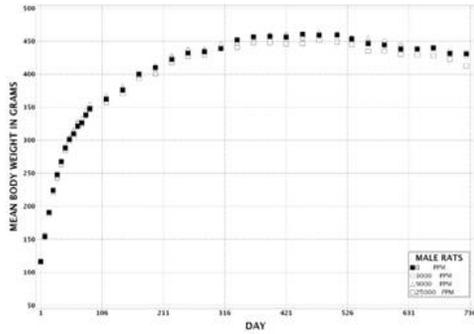


2-Year Study - Survival - Rats





2-Year Study - Body Weights - Rats





2-Year Study - Nonneoplastic Liver Lesions - Rats

Dose (ppm)	0	3000	9000	25,000
Male rats				
Hepatocyte, hypertrophy	0	19** (1.4) ^a	31** (1.9)	27** (2.6)
Hepatocyte, degeneration	0	22** (1.1)	30** (1.8)	19** (2.3)
Eosinophilic focus	4	5	25**	28**
Female rats				
Hepatocyte, hypertrophy	2 (2.0)	10* (1.3)	27** (1.5)	38** (2.1)
Hepatocyte, degeneration	1 (1.0)	2 (1.0)	12** (1.1)	24** (1.3)
Eosinophilic focus	2	24**	29**	22**

^aSeverity Grade * p ≤ 0.05 **p ≤ 0.01

N=50 per group



2-Year Study - Neoplastic Liver Lesions - Male Rats

Dose (ppm)	0	3000	9000	25,000
Male rats				
Cardiomyopathy	47* (2.0)	38 (1.9)	39 (2.1)	36* (1.8)
Female rats				
Cardiomyopathy	24* (1.5)	24 (1.3)	21 (1.3)	15* (1.3)

^aTrend statistic ^bPairwise statistic
**p ≤ 0.01

N=50 per group



2-Year Study - Neoplastic Liver Lesions – Male Rats

Dose (ppm)	0	3000	9000	25,000
Hepatocellular adenoma, multiple	0	0	0	2
Hepatocellular adenoma (includes multiple)	1** (729)	1 (684)	2 (663)	10** (612)
Hepatocellular carcinoma	0	0	0	1
Hepatocellular adenoma or carcinoma	1**	1	2	11**

**p ≤ 0.01

N=50 per group



2-Year Study - Neoplastic Liver Lesions - Female Rats

Dose (ppm)	0	3000	9000	25,000
Hepatocellular adenoma	0**	0	1	8**

**p ≤ 0.01

N=50 per group



2-Year Study - Mammary Gland Lesions - Female Rats

Dose (ppm)	0	3000	9000	25,000
Hyperplasia	49	46	45	34**
Fibroadenoma (multiple)	8	3	4	1**
Fibroadenoma (includes multiple) ^c	30**	20*	11**	17**

* $p \leq 0.05$ ** $p \leq 0.01$

N=50 per group



2-Year Study - Heart Lesions - Rats

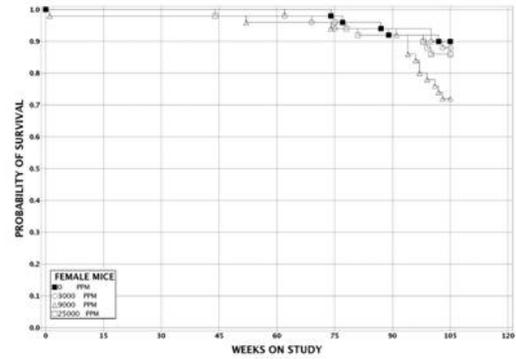
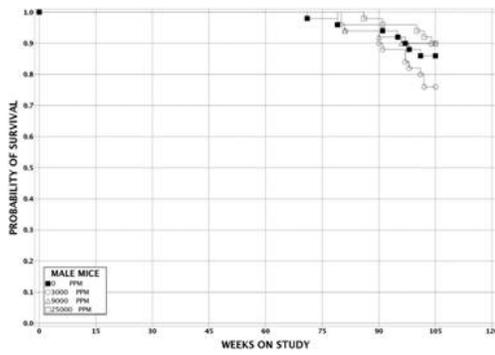
Dose (ppm)	0	3000	9000	25,000
Male rats				
Cardiomyopathy	47* (2.0)	38 (1.9)	39 (2.1)	36* (1.8)
Female rats				
Cardiomyopathy	24* (1.5)	24 (1.3)	21 (1.3)	15* (1.3)

* $p \leq 0.05$

N=50 per group

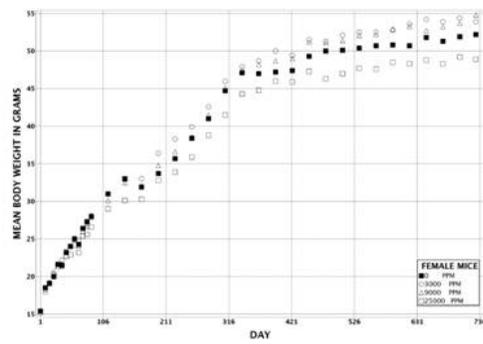
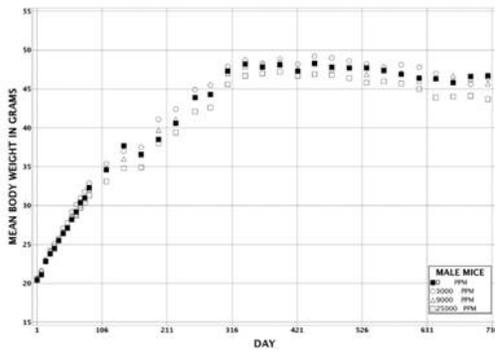


2-Year Study - Survival - Mice





2-Year Study - Body weights - Mice



2-Year Study - Nonneoplastic & Neoplastic Liver Lesions - Male Mice

Dose (ppm)	0	3000	9000	25,000
Eosinophilic focus	7	14	14	24**
Hepatoblastoma (multiple)	0	0	0	2
Hepatoblastoma (includes multiple)	1*	2	1	6
Hepatocellular adenoma (multiple)	3	5	11*	18**
Hepatocellular adenoma (includes multiple)	22*	16	23	29

* $p \leq 0.05$ ** $p \leq 0.01$

N=50 per group



2-Year Study - Neoplastic Liver Lesions - Male Mice (continued)

Dose (ppm)	0	3000	9000	25,000
Hepatocellular carcinoma (includes multiple)	8	14	15	12
Hepatocellular adenoma, carcinoma, or hepatoblastoma 50%(36%-64%) ^a	26 52%	28 56%	31 62%	33 66%

Historical data (feed):

N=50 per group

^a125/250 (50.0% ± 10.2%), range 36%-64%



2-Year Study - Neoplastic Liver Lesions - Female Mice

Dose (ppm)	0	3000	9000	25,000
Hepatocellular adenoma (multiple)	0	0	1	2
Hepatocellular adenoma (includes multiple) <i>6.7%(2%-10%)^a</i>	3 <i>6%</i>	6 <i>12%</i>	7 <i>14%</i>	7 <i>14%</i>

Historical data (feed):

^a20/300 (6.7% ± 2.7%), range 2%-10%

n=50 per group



Conclusions

- Male rats: **clear** evidence of carcinogenic activity
 - Increased incidences of hepatocellular adenoma and hepatocellular adenoma or carcinoma (combined)
- Female rats: **clear** evidence of carcinogenic activity
 - Increased incidences of hepatocellular adenoma
- Male mice: **some** evidence of carcinogenic activity
 - Increased incidences of hepatoblastoma and multiple hepatocellular adenoma
- Female mice: **no** evidence of carcinogenic activity